IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) : Anderson, et al.
SERIAL NO. : 10/068,635
FILED : February 05, 2002
FOR : 2-Amino-9H-purin-9-yl Compounds and Methods for Inhibiting/Treating HIV Infections and AIDS Related Symptoms (As amended)
GROUP ART UNIT : 1624
Examiner : Thomas C. McKenzie

MailDrop: Non-fee Amendment
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

**Declaration of Dr. Karen Anderson**

SIR:

1. I, Karen S. Anderson, declare as follows:

2. I am a citizen of the United States of America.

3. I am a co-inventor of the subject matter of the above-referenced patent application.

4. I have over 20 years experience as a Ph.D. level researcher in the pharmaceutical/biological sciences.

5. I am the Director of Medical Studies, in the Department of Pharmacology, Yale University School of Medicine, New Haven, CT, and have held that position since early 2000.

6. Since that same time in 2000, I have been a Professor with tenure, Department of Pharmacology Yale University School of Medicine, New Haven, CT.

7. From 1993-2000 I was an Associate Professor, in the Department of Pharmacology Yale University School of Medicine, New Haven, CT. During that same period in 1998-2000, I was a tenured Associate Professor.

8. From 1990-1993 I was an Assistant Professor, in the Department of Pharmacology Yale University School of Medicine, New Haven, CT.

9. From 1982 until 1989, I was a research scientist at Monsanto Agricultural Products, St. Louis, Missouri, first in the Metabolism Division (1982-1986) and then in the Herbicide Discovery Division (1986-1989).

10. I received my B.S. in microbiology in 1977 from East Tennessee State University in Johnson City, Tennessee.

11. I received my Ph.D. in Medicinal Chemistry in 1982 from the Ohio State University, Columbus, Ohio.

12. My areas of technical expertise include the following:
- Protein structure-function and mechanistic enzymology;
- Non-nucleoside and Nucleoside Inhibitors of reverse transcriptase in HIV;
- Drug Resistance in HIV;
- Analysis of Enzyme Intermediates; and
- Probing Mechanisms of Substrate Channeling.

13. I have published over ninety (90) technical articles, a number of which articles relate to mechanistic studies on and inhibition of enzymes and in particular, reverse transcriptase in HIV.

14. I have received numerous honors and awards including:

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| 1978-81 | National Institute of Health Predoctoral Fellowship |
| 1981-82 | American Foundation for Pharmaceutical Education Fellowship |
| 1982 | Phi Kappa Phi |
| 1982 | Research Award, Eighth Annual ICSABER Forum for Graduate Students |
| 1985 | Monsanto Research Achievement Award |
| 1986 | YWCA Women's Leadership Award |
| 1987 | Monsanto Research Achievement Award |
| 1987 | YWCA Women's Leadership Award |
| 1988 | Monsanto Research Achievement Award |
| 1989 | Monsanto Research Achievement Award |
| 1990 | Hull Cancer Research Award, Yale University |
| 1991 | Dean's Young Faculty Award, Yale University |
| 1991 | Nominating Committee, Biological Division of Am.Chem.Soc. |
| 1992 | East Tennessee State University Alumni Award |
| 1994-98 | NIH Biochemistry Study Section Member |
| 1996 | Yale Cancer Breast Cancer Initiative Research Award |
| 1999 | American Cancer Society, Cancer Drugs & Development Study Section |
| 1999-03 | NIH AIDS (AAR3) Study Section Member |

2000 Co-Vice Chair, Enzymes Gordon Research Conference
2001 Co-Chair, Enzymes Gordon Research Conference
2002 Ohio State Distinguished Alumni Award

15. As a co-inventor of the subject matter of patent application number serial number 10/068,635, I am familiar with the subject matter presently claimed. I understand that my invention as set forth in pending claims 1-30 is directed to compounds, compositions and methods which make use of certain nucleoside analogs which may be used in effective amounts to inhibit the growth, elaboration and/or the replication of HIV in a patient or will reduce the likelihood that an individual will contract HIV or that an HIV infection will mature into AIDS in a patient.

16. I have read the Examiner's office action dated June 18, 2003 and understand that the Examiner, in paragraphs 13 on page 10 of that office action questions the type of virus which was used in the experiments and the results which are presented on pages 23-29 and in figures 2-4 and the implications for the results of those experiments. I have reviewed the Biological Experiments section of the present application which appears on pages 23-29 and the results which are set forth on those pages as well as figures 2-4 of the present application. The experiments which are described on pages 23-29 were conducted in my laboratory at Yale University under my direction and supervision.

17. In the experiments which are set forth on those pages, experiments were conducted to determine the activity of compound 9 (Figure 1, the cyclopropylamine analog) against HIV. Apparently what has confused the Examiner is the statement in the fourth line of the first full paragraph under the heading **"Anti-HIV Activity"** is the statement that the MT-2 cell line "is productively infected with Human T Cell Leukemia Virus (HTLV)". Although this statement is accurate, it nevertheless has confusingly led to the conclusion by the Examiner that the experiments were directed to HTLV inhibition, not HIV. A more appropriate wording should be that the MT-2 cells are "chronically-infected" with HTLV. Upon subsequent acute infection with **HIV (strain IIIB)** the cells show marked morphological changes including syncytia formation that can be detected microscopically and with the addition of methylthiotetrazolium (MTT) dye as a result of the presence of HIV viral replication. This is a standard cell line and protocol used by all HIV researchers and the presence of the chronic HTLV infection enables one to detect very distinct cellular changes when acutely infected by HIV. All the assays used employed the HIV virus. After my review, I can unequivocally state that the experiments which are presented on pages 23-29 are specifically directed to HIV inhibition, not HTLV inhibition. Furthermore, the results presented on those pages evidence that compound 9 exhibits exceptional inhibition of HIV and rather limited toxicity, evidencing that the compound is expected to be useful as a clinical anti-HIV agent exhibiting reduced toxicity to the

patient (host). Moreover this compound has good antiviral activity against a number of drug-resistant mutant HIV viruses including the M184V associated with 3TC- drug resistance as well as mutant HIV virus associated with AZT drug resistance. Finally, compound 9 displays synergistic antiviral activity when tested in HIV-infected cell culture when tested with a number of other AIDS drugs currently on the market including AZT, 3TC, nevirapine, and protease inhibitors defining a useful role in combination or HAART (highly active antiretroviral therapy) therapy.

18. I further declare that all statements made herein of my own personal knowledge are rue and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 11/14/03 Karen S. Anderson

Karen S. Anderson

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The Stamp of the United States Patent Office
Acknowledges receipt of the following documents
entitled: Patent Application(s) of ANDERSON,
Karen, et al. Application No. 10/068,635

PETITION FOR EXTENSION
AMENDMENT/RESPONSE (18 PAGES)
DECLARATION OF DR. KAREN ANDERSON
CHECK # 2352 in the sum of Two Hundred Dollars
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